Kidney International, Vol. 48 (1995), pp. 851–859

"Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis

ROBERT D. TOTO, HELEN C. MITCHELL, RONALD D. SMITH, HING-CHUNG LEE, DONALD MCINTIRE, and WILLIAM A. PETTINGER

Department of Internal Medidcine and Biostatistics, The University of Texas Southwestern Medical Center-Dallas, and The Dallas Nephrology Research Institute, Dallas, Texas; and Midwest Hypertension Research Center at Creighton, Omaha, Nebraska, USA

"Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. Hypertensive nephrosclerosis is a progressive renal disease and the leading cause of end-stage renal disease (ESRD) in blacks in the United States. It is generally believed that hypertensive renal injury is responsible for progressive renal failure; however, it is not known whether pharmacologic lowering of blood pressure to any level prevents progression of renal disease. Accordingly, we performed a long-term prospective randomized trial to determine whether "strict" [diastolic blood pressure (DBP) 65 to 80 mm Hg] versus "conventional" (DBP 85 to 95 mm Hg) blood pressure control is associated with a slower rate of decline in glomerular filtration rate. Eighty-seven non-diabetic patients (age 25 to 73; 68 black, 58 male) with long-standing hypertension (DBP $\geq$ 95 mm Hg), chronic renal insufficiency (GFR $\leq$ 70 m/min/1.73 m^2) and a normal urine sediment were studied. DBP was pharmacologically lowered to $\leq$ 80 mm Hg (3 of 4 consecutive measurements at 1 to 4 weeks intervals) after which patients were randomized. DBP and GFR (renal clearance of ^{125}I-iothalamate) were measured at baseline, at three months and every six months post-randomization. The rate of decline in GFR (GFR slope, in ml/min/1.73 m^2/year), estimated by the method of maximum likelihood in a mixed effects model, was the primary outcome variable. In a secondary analysis, 50% reduction in GFR (or a doubling of serum creatinine) from baseline, ESRD and death were combined. Also the rate of decline in GFR in blacks and non-blacks was compared. Mean follow-up was 40.5 $\pm$ 1.8 months in the "strict" and 42.2 $\pm$ 2.1 month in the "conventional" groups. Mean follow-up DBP was 81 $\pm$ 1 mm Hg in the "strict" and 87 $\pm$ 1 mm Hg in the "conventional" groups ($P < 0.0001$, 95% C.I. for the difference -8.4 to -3.1). GFR slope was -0.31 ± 0.45 in the "strict" and -0.050 ± 0.50 ml/min/1.73 m^2/year in the "conventional" group ($P > 0.25$, 95% C.I. for the difference -1.60 to 1.08). The mean slopes were not significantly different from zero. Twelve (7 with ESRD) of 42 "strict" and 7 (2 with ESRD) of 35 "conventional" (2 ESRD) patients experienced a clinical endpoint in the time to event analysis ($P > 0.25$). Mean follow-up DBP was 85 $\pm$ 1 in blacks and 79 $\pm$ 1 in non-blacks ($P < 0.01$, 95% C.I. 2.3 to 9.8); however, GFR slope in blacks ($N = 58$) was -0.016 ± 0.37 versus -0.27 ± 0.76 ml/min/1.73 m^2/year in non-blacks ($P > 0.25$). We conclude that in hypertensive nephrosclerosis "strict" control of blood pressure to a mean DBP of 81 $\pm$ 0.8 mm Hg did not conserve renal function better than "conventional" control of blood pressure to a mean of 86.7 $\pm$ 1.1 mm Hg. However, both "strict" and "conventional" blood pressure control are associated with a very slow overall mean rate of decline in GFR. In addition, we found that long-term blood pressure lowering was associated with a similar slow rate of decline in GFR in blacks and non-blacks. Application of this quality of blood pressure control could significantly reduce the incidence of ESRD in the United States.

Received for publication November 7, 1994
and in revised form April 17, 1995
Accepted for publication April 17, 1995

Hypertensive nephrosclerosis is a progressive renal disease, and the leading cause of end-stage renal disease (ESRD) in blacks [1, 2]. Prospective studies in predominantly black male populations carried out in the 1950's and 1960's demonstrated that untreated hypertension carries a substantial risk of ESRD [3, 4]. Subsequent studies in treated hypertensive nephrosclerosis indicated that chronic renal insufficiency, that is, serum creatinine > 1.5 mg/dl, is the most important risk factor for progressive renal damage in hypertensive nephrosclerosis [3–6]. In addition, higher blood pressure [3, 4, 7–9], black race [2, 5, 7, 10–13], male sex and older age are all independently associated with increased risk for ESRD [1, 5, 8, 11, 12, 14]. Moreover, these studies suggest that long-term lowering of blood pressure in high-risk patients should preserve renal function and lower ESRD risk.

In the early 1970's, bilateral nephrectomy became a standard form of therapy for patients with severe refractory hypertension and hypertensive nephrosclerosis [15]. Improved pharmacological therapy, notably the introduction of minoxidil, eliminated the need for this drastic procedure. In some cases treatment with minoxidil reduced the rate of decay of renal function, prolonging considerably the time interval to hemodialysis [16]. However, nearly 1/3 of patients whose blood pressure was lowered to the level of 160/100 continued to have declining renal function, and far too many progressed to ESRD. The key question is to what level should blood pressure be reduced to maintain renal function in patients with hypertensive nephrosclerosis and established renal insufficiency.

Lowering blood pressure in hypertensives has been shown to reduce mortality due to stroke and myocardial infarction [3, 17–20], but the incidence of ESRD has increased [1, 2, 14, 21]. Furthermore, it has been suggested that lowering diastolic blood pressure to $\leq$ 90 mm Hg protects the brain and heart, but not the kidneys [22]. Studies performed in the 1950's and 1960's showed that in comparison to placebo or untreated controls, pharmacologic lowering of diastolic blood pressure to 95 to 100 mm Hg did not preserve renal function [3, 4, 23]. Extremely high morbidity and mortality rates precluded further placebo-controlled trials. Subsequent studies in treated patients with mild to moderate hypertension suggested that blood pressure lowering may preserve renal function [5, 8, 12, 16, 23, 24]. However, none of these studies specifically examined the effect of long-term blood pressure lowering on renal function. Moreover, no prospective study has carefully delineated the rate of decline in renal function or

rate of ESRD in treated patients with hypertensive nephrosclerosis. In a previous report from our institution, Pettinger et al demonstrated that short-term "strict" followed by long-term "conventional" control of diastolic blood pressure (DBP) in a subset of 22 patients was associated with improvement in GFR followed for 36 months [25]. We hypothesized that chronic lowering of diastolic blood pressure to physiologic levels would slow the decline in GFR to a greater extent than a higher but "normal" level. Accordingly, we performed a long-term prospective randomized trial to determine whether "strict" (diastolic blood pressure, DBP 65 to 80 mm Hg) versus "conventional" (DBP 85 to 95 mm Hg) control of blood pressure is associated with a slower rate of decline in GFR. To accomplish this, we measured the rate of progression of renal disease in 87 patients with hypertensive nephrosclerosis and reduced renal function by serial measurement of GFR over an average period of 40 months. Patients with renal insufficiency (S_{Cr} > 1.6 mg/dl) were chosen because of their high-risk for progressive renal disease [3–5, 26].

Methods

Patients

We recruited eighty-seven patients ranging in age from 25 to 73 with hypertensive nephrosclerosis. Patients were included in the study if they had a diastolic blood pressure ≥ 95 mm Hg, a serum creatinine of > 1.6 mg/dl and a GFR of ≤ 70 ml/min/1.73 m^2, a history of long-standing hypertension, an inactive urine sediment, a protein excretion rate of ≤ 2 g/day, and no physical or biochemical evidence for a humoral-mediated cause for hypertension. Patients with diabetes mellitus, a recent history (<4 months) of malignant hypertension, stroke or myocardial infarction, acute renal failure of any cause, analgesic abuse, polycystic kidney disease, systemic lupus erythematosus, scleroderma, rapidly progressive glomerulonephritis, evidence of significant hepatic impairment (AST and ALT greater than 2.5 × normal or serum total bilirubin > 1.5 mg/dl), mental incapacity, pregnancy or lactation, primary aldosteronism, renovascular hypertension, pheochromocytoma, or a serum creatinine > 7.0 mg/dl were excluded. Demonstration of progression of renal disease prior to entry was not required. The study was approved by the local Institutional Review Board and written informed consent was obtained from all participants.

Experimental design

Initial assessment period. Before randomization, DBP was lowered to ≤ 80 mm Hg over a three to six month initial assessment period. To achieve this goal, participants were administered antihypertensive medications using a stepped-care approach as follows: (Step 1) diuretic; (Step 2) β-blocker; (Step 3) hydralazine or minoxidil; and (Step 4) clonidine, α-methyldopa or α_1-blocker. In general the maximum dose of each agent (except diuretic) was used before moving to the next step. Patients were considered "responders" if on three of four consecutive clinic visits the DBP was ≤ 80 mm Hg during this period. Based on this criterion, 77 patients were "responders" and 10 were "non-responders".

Randomization and intervention. The study was a 2 × 2 factorial, randomized double-blind placebo-controlled trial. After completion of the initial assessment period, "responders" were randomized to either placebo or enalapril and to either "strict" 65 to 80 mm Hg and "conventional" 85 to 95 mm Hg blood pressure ranges. These two ranges of DBP were chosen in an attempt to achieve a mean difference of 10 mm Hg in DBP between groups while maintaining DBP below 95 mm Hg in all patients. The lower level of 65 to 80 mm Hg was chosen to emulate a "physiologic" DBP level. Thus, in patients assigned to "conventional" group, we allowed DBP to increase to the 85 to 95 mm Hg range whereas in patients assigned to the "strict" group we attempted to maintain DBP in the 65 to 80 mm Hg range. The 10 patients who did not achieve the DBP goal of ≤ 80 mm Hg ("non-responders") were not randomized but were followed-up with an attempt to maintain DBP in the 85 to 95 range. Baseline characteristics for these "non-responders" (data not shown) were similar and not significantly different as compared to randomized patients. Because assignment to enalapril versus placebo did not change the results of the blood pressure control, this report describes the results of blood pressure control only. Blood pressure medications were titrated in the same manner in both placebo and enalapril treated groups.

Follow-up procedures and measurements

Blood pressure control. Patients were followed at 12 week intervals. Additional visits for blood pressure measurement and medication adjustment were performed in an attempt to maintain DBP in the assigned range throughout the follow-up period. After randomization, 23 patients in the "strict" and 18 patients in the "conventional" group received enalapril in addition to the stepped-care antihypertensive regimen. The blinded study drug was titrated to the maximum allowable dose and the unblinded antihypertensive(s) were back-titrated as needed to achieve and maintain blood pressure control. The titration procedure was identical for both drug and blood pressure control arms of the study. Compliance with the study medications was assessed at each visit by patient interview and pill counting.

Measurement of blood pressure. Resting blood pressure was measured after a minimum of five minutes in the supine position using a standard mercury sphygmomanometer. The mean of three measurements taken at two minute intervals was used for making medication adjustments during baseline and post-randomization periods. Systolic blood pressure (SBP) was determined as the initial Korotkoff sound (phase I) and the DBP was determined at the disappearance of Korotkoff sounds (phase V). Blood pressure was measured on the day of the GFR in 90% of instances and within one week of the GFR in all cases.

Measurement of renal function. Glomerular filtration rate and serum creatinine were measured at the following specified intervals: baseline (pre-randomization) and at 3, 9, 12, 18, 24, 36, 42, 48, 54 and 60 months post-randomization. Twenty-four hour urine protein excretion rate was measured at six-month intervals during follow-up. Serum and urine creatinine and urine protein concentrations were measured by automated methods (Smith, Kline and Beecham Laboratories, Dallas, TX, USA).

GFR was measured by renal clearance of ^{125}I-iothalamate as previously described [25, 27]. Briefly, an oral water load of 20 ml/kg and 10 drops of saturated potassium iodide were administered. After a minimum of 45 minutes, 35 μCi of ^{125}I-iothalamate was injected subcutaneously and the average of three 30-minute urinary collections with midpoint blood samples was used to calculate GFR. GFR was corrected for body surface area and expressed in ml/min/1.73 m^2. In our laboratory the intra-assay coefficient of variation was 13 ± 7%. The interassay coefficient of

variation (3-month interval) for patients with GFR in the range of 25 to 70 ml/min/1.73 m^2 was 12 ± 4%.

Statistical methods and data analysis

Power calculations. During the planning phase of this trial the baseline rate of decline in renal function for the "conventional" group was unknown. The effect size was based on an expected mean difference in the rate of decline in GFR of 4 ml/min/year. Using a standard deviation of 6 ml/min/year, an α of 0.05, and a power of 0.85 we calculated that 40 patients per group would be required to detect this difference.

Measurement of change in renal function. The data were analyzed according to the principle of intention-to-treat. The rate of decline in GFR (GFR slope in ml/min/1.73 m^2/year) was the primary outcome measure in this study. At least three GFR measurements were considered necessary to calculate a valid GFR slope and all patients met this criterion (mean = 7, range 3 to 11) [28]. The rate of decline in GFR for each group was estimated by the method of maximum likelihood in a mixed effects model which takes into account differences in duration of follow-up among patients [29]. The estimated decline in GFR was also calculated by the model after accounting for potential predictors of declining GFR at baseline including age, race, gender, serum creatinine and 24-hour urine protein excretion rate. The data presented in Tables and Figures represent the mean rate of change in GFR estimated by this method. In addition, based on the experience of the Modification of Diet in Renal Disease (MDRD) trial [30], we also evaluated the rate of change in GFR using a piece-wise two-slope linear model in which the effect of the first three months of (post-randomization) intervention on the overall change in GFR within study groups was evaluated. This piece-wise linear model estimates the slopes from zero to three months (initial) and from three months until the end of follow-up (terminal). The purpose of this analysis was to assess whether the acute (first 3 months) effect of blood pressure control results in differences in the magnitude and/or direction of initial as compared to terminal GFR slope and how such differences might affect overall slope. The mean of the individual patient slopes over these periods of time were computed as previously reported [30]. All GFR and S_{Cr} measurements obtained at the intervals noted above were used in these calculations. Standard two-stage regression was performed on the rate of decline in reciprocal of serum creatinine in which the slope was estimated by least squares, and these slopes were treated as outcome variables for mean, SDS, and *t*-tests.

Secondary analyses included comparison of GFR slope after combining groups together, comparison of patients with baseline 24-hour urine protein rate > 500 mg versus < 500 mg and comparison of black versus non-black patients. In the latter comparison, GFR slope was calculated after adjusting for baseline values (see above) as well as for differences in follow-up mean blood pressure level. In addition, we performed a retrospective combined time to event analysis to evaluate the impact of the intervention on renal events and death. In this analysis, patient demise was defined as the occurrence of any of the following: doubling of serum creatinine from baseline, a 50% reduction of GFR from baseline, ESRD, and death. ESRD was defined as need for either dialysis or renal transplantation in patients with symptomatic uremia and a GFR ≤ 15 ml/min/1.73 m^2.

Student's *t*-test was used to test for differences between group means for specific variables and to determine whether individual patient GFR slopes were different from zero. Ninety-five percent confidence intervals for the differences in mean values were calculated when appropriate. Fisher's exact test and Chi-square test with Yates correction were used for comparison of nominal data. In the time to event analysis, a Kaplan-Meier plot was constructed and the data analyzed by log-rank test for differences in survival times between randomized groups. A P value of < 0.05 or less was considered significant and all statistical analysis employed two-tailed tests of significance. Data in tables are mean ± SEM. There were no significant interactions between blood pressure control groups and randomized drug group assignment, that is, enalapril versus placebo and the rate of decline in GFR. Therefore the results presented are confined to the effects of blood pressure control groups on decline in GFR.

Table 1. Baseline characteristics of patients at randomization

Characteristic	Strict (N = 42)	Conventional (N = 35)	Entire group (N = 77)
Age *years*	55.8 ± 1.5	55.7 ± 1.6	55.7 ± 1.1
Race *black/non-black*	29/13	29/6	58/19
Sex *F/M*	20/22[a]	9/26	29/48
Body mass index *kg/m²*	28.9 ± 0.9	28.2 ± 1.0	28.7 ± 0.7
Systolic BP *mm Hg*	124 ± 2	122 ± 3	123 ± 2
Diastolic BP *mm Hg*	76 ± 1	77 ± 1	76 ± 1
Mean arterial pressure *mm Hg*	92 ± 1	92 ± 2	92 ± 1
Serum creatinine *mg/dl*	2.5 ± 0.2	2.1 ± 0.1	2.3 ± 0.1
Glomerular filtration rate *ml/min/1.73 m²*	34.6 ± 2.3	41.9 ± 3.1	37.8 ± 1.8
Urine protein excretion rate *mg/day*	373 ± 59	344 ± 82	359 ± 49
Antihypertensive medications (No.)[b]	2.7 ± 0.2	2.6 ± 0.2	2.7 ± 0.1
Cardiovascular complications[c]	14	14	28

[a] Strict vs. Conventional, $P < 0.05$ (Chi-square test)
[b] Number of antihypertensive medications at baseline
[c] Previous cardiovascular complications including angina pectoris, myocardial infarction, congestive heart failure and cerebrovascular accident.

Results

Baseline characteristics

Baseline characteristics of 77 randomized patients at the time of randomization are shown in Table 1. The majority of the patients (53 of 77) had at least 36 months of follow-up. The patients were predominantly black (75%), mostly male (63%) and had a high rate (28 of 77) of cardiovascular complications prior to randomization. The female-to-male ratio was significantly higher in "strict" versus "conventional" patients. Baseline mean GFR was slightly lower at 34.6 ± 2.3 ml/min/1.73 m^2 in the "strict" as compared to 41.9 ± 3.1 in the "conventional" group, however, this difference was not statistically significant.

Follow-up

Primary analysis. The mean follow-up values for blood pressure, renal function and outcome are shown in Table 2. Mean systolic blood pressure was slightly lower in "strict" as compared with "conventional" group but the difference was not significant (P = 0.11). In contrast, both mean DBP and mean MAP were significantly lower in the "strict" group (Table 2). Mean DBP was 81 ±

Table 2. Blood pressure control and renal function during follow-up in hypertensive nephrosclerosis

Parameter	Strict ($N = 42$)	Conventional ($N = 35$)	Entire group ($N = 77$)
Blood pressure			
Systolic BP *mm Hg*	133 ± 3	138 ± 2	135 ± 2
Diastolic BP *mm Hg*	81 ± 1	87 ± 1[a]	84 ± 1
Mean arterial pressure *mm Hg*	98 ± 1	104 ± 1[b]	101 ± 1
Renal function			
Rate of decline in GFR *ml/min/1.73 m²/year*	−0.31 ± 0.45	−0.05 ± 0.50	−0.002 ± 0.10
Rate of decline in $1/S_{Cr}$ *dl/mg/month* × 10^{-3}	−1.9 ± 0.6	−0.5 ± 0.8	−1.4 ± 0.6
Final serum creatinine *mg/dl*	3.0 ± 0.4	2.6 ± 0.3	2.8 ± 0.2
Change in serum creatinine from baseline *mg/dl*	0.49 ± 0.22	0.44 ± 0.26	0.46 ± 0.23
Event			
50% decline in GFR or doubled serum creatinine (from baseline)	4	5	9
End-stage renal disease	7	2	9
Death	1	0	1
Total #	12	7	19
Duration of follow-up *months*	40.5 ± 1.8	42.2 ± 2.1	41.3 ± 1.6

Abbreviations are in Table 1. The rate of decline in GFR was estimated by the method of maximal likelihood in a mixed effects model. The mean value represents the best linear unbiased predictors of the rate of change in GFR.

[a] $P < 0.0001$ compared with "strict" group

[b] $P < 0.003$ compared with "conventional" group

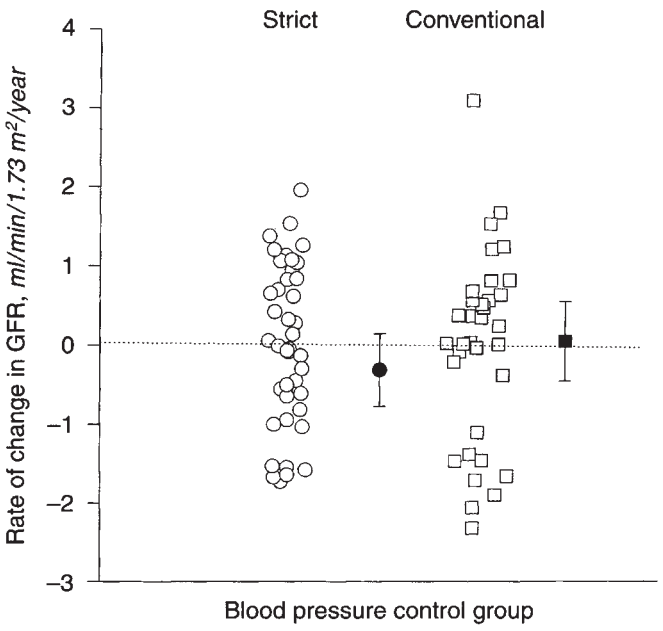

Fig. 1. *Distribution of change in GFR estimated by the mixed effects model for blood pressure control groups.* The individual patient slopes (open symbols) represent the best linear unbiased predictors of the rate of change in GFR. Closed symbols are mean ± SEM. The mean rate of decline in GFR was not significantly different between groups.

1 in the "strict" group and 87 ± 1 mm Hg in the "conventional" group. The mean difference for DBP was 5.7 mm Hg ($P < 0.0001$, 95% C.I. −8.35 to −3.05) and for MAP was 5.5 mm Hg ($P < 0.003$, 95% C.I. −9.03 to −1.97). The mean rate of decline in GFR for the "strict" group was −0.31 ± 0.45 ml/min/1.73 m²/year (range −1.73 to +1.95) and for the "conventional" group was −0.05 ± 0.50 (range −2.32 to +3.09) ml/min/1.73 m²/year (Table 2, Fig. 1). The mean rate of decline in GFR for "strict" and "conventional" groups were not significantly different from one another. Neither rate of decline in GFR was significantly different from zero ($P > 0.25$). The 95% confidence interval for the mean difference in rate of decline in GFR was −1.60 to + 1.09. The rate of decline in GFR estimated after running the model with baseline age, race, sex, serum creatinine and 24-hour urine protein excretion rate as covariates was −0.13 ± 0.46 in the "strict" group and +0.010 ± 0.50 ml/min/1.73 m²/year ($P > 0.25$) in the "conventional" group.

As shown in Figure 1, there was considerable variability in the rate of change in GFR within groups; however, most patients exhibited either an improvement or only a slow decline in GFR (≤ −1 ml/min/1.73 m²/year). The mean difference between initial and final GFR in the "strict" group was −2.2 ± 1.9 ml/min/1.73 m²/year and +1.5 ± 2.8 ml/min/1.73 m²/year in the "conventional" group. The slightly positive mean difference in GFR in the conventional group, despite a negative mean slope, probably reflects the variability in duration of follow-up among study patients.

It is known that "acute" changes in GFR may accompany alterations in blood pressure during the immediate post-randomization period [28]. Therefore, we analyzed the change in GFR over time by dividing the slope into two components: (1) an "acute" slope of zero to three months and (2) a "chronic" slope consisting of three months to end of follow-up (statistical analysis under **Methods** section). As shown in Figure 2 the apparent overall slower decline in GFR in the "conventional" group was due in part to an increase in GFR during the first three months followed by a trend toward a greater decline in GFR during the remainder of follow-up. In contrast, in the "strict" group, GFR increased only slightly during the first three months followed by a much slower overall decline during the remainder of follow-up. Table 3 illustrates the "acute", "chronic" and total rate of change in GFR for the blood pressure control groups. There were no significant differences between groups for the initial (0 to 3 months) or the terminal (3 months to end of follow-up) slopes. However, as shown in the table, to some extent the acute effect of blood pressure changes during the first three months altered the overall slope of the GFR so that during the long-term, GFR deteriorated at a slightly, although not significantly, greater rate in the "conventional" group.

Secondary analysis: "Strict" and "conventional" groups combined. The overall mean rate of progression for both groups combined was −0.008 ± 0.25 ml/min/1.73 m²/year. This indicates that the overall mean rate of decline in GFR for the population is quite slow. However, the correlation between GFR slope and mean follow-up blood pressure after controlling for baseline predictors of progression including age, race, sex, baseline GFR and baseline protein excretion rate was poor. The correlation coefficient for this relationship for GFR slope and mean follow-up diastolic blood pressure was 0.050 ($P = 0.21$). It should be noted that the range of mean diastolic blood pressures over which the regression is carried out is relatively narrow (65 to 90 mm Hg) and

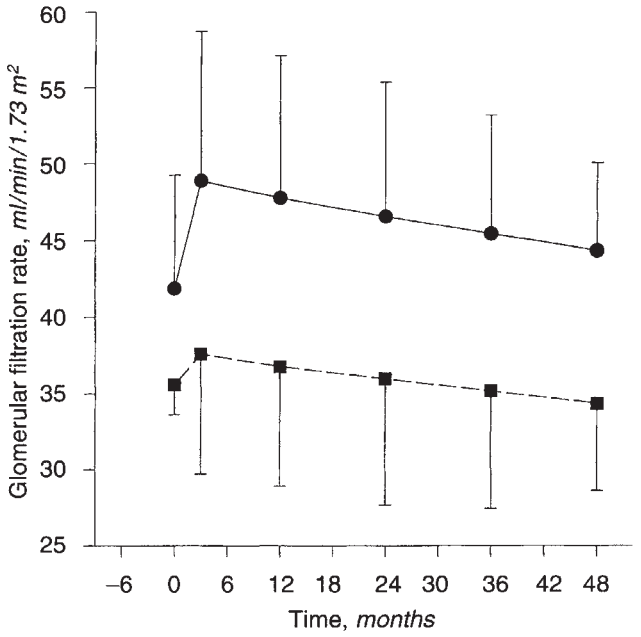

Fig. 2. *Estimated rate of change in GFR (mixed effects model, Methods section) for blood pressure control groups during follow-up.* Symbols are: (●) "conventional", (■) "strict" groups. The rate of change in GFR is fitted to a two-slope piece-wise model as previously described [30]. There is a trend for the decline in GFR after three months of follow-up to be slightly slower in the "strict" group as compared to the "conventional" group, however, the difference is not significant. The bars represent 95% confidence intervals for GFR estimates.

that 75 of 77 patients had mean DBP values were at or below 95 mm Hg.

Combined endpoints

Four of 42 "strict" and five of 35 "conventional" patients experienced either a 50% decline in GFR or a doubling of serum creatinine during follow-up, and six of these patients developed ESRD. Three patients developed ESRD without doubling creatinine or experiencing a 50% decline in GFR. As shown in Figure 3, there were no differences between groups in the time to event analysis. Of the nine patients who developed ESRD, seven were in the "strict" and two in the "conventional" group, an incidence rate of about 4%/year (9 of 77 over 3½ years; Table 2). The duration of follow-up in patients with ESRD averaged 33 ± four months and ranged from 18 to 54 months. The incidence of ESRD was not different between groups ($P > 0.25$). Baseline mean GFR was 19.3 ± 5.3 ml/min/1.73 m^2 (range 9.7 to 54) in patients who developed ESRD as compared to 39.6 ± 5.4 ml/min/1.73 m^2 patients who did not progress to ESRD ($P < 0.001$, 95% C.I. −36.3 to −14.9). However, mean systolic (136 ± 2) and diastolic (80 ± 0.1) BP in ESRD patients were not significantly different from non-ESRD patients. There was one death ("strict" group) during the study.

Mean $1/S_{Cr}$ slope was −0.0019 ± 0.0006 in the "strict" and −0.0005 ± 0.0008 in the "conventional" groups. These slopes were not significantly different from each other or from zero (Table 2).

Table 3. Rate of change in GFR from 0 to 3 months ("acute slope"), 3 months to end of study ("chronic slope"), and from 0 to end of study ("total slope")

Group	Rate of change in GFR *ml/min/1.73 m²/year*		
	Acute	Chronic	Total
Strict ($N = 42$)	1.4 ± 8.7	−0.38 ± 0.50	−0.31 ± 0.45
Conventional ($N = 35$)	15.3 ± 9.8	−0.60 ± 0.55	−0.05 ± 0.50

Mean rate of change in GFR (GFR slope) is calculated using the method of maximal likelihood in a mixed effects model. There were no significant differences in GFR slopes between groups.

Proteinuria

We compared the rate of change in GFR in 17 patients with a baseline 24-hour urine protein excretion rate of > 500 mg to that of 60 patients whose baseline 24-hour urine protein excretion rate was < 500 mg. Mean rate of decline in GFR in patients with > 500 mg/day was −2.1 ± 0.80 and in patients with < 500 mg/day was +0.28 ± 0.35 ml/min/1.73 m^2/year ($P < 0.01$, 95% C.I. for the difference −3.94 to −0.82). There was a significant negative correlation between GFR slope and baseline proteinuria in patients with baseline protein excretion > 500 mg/day ($r = 0.53$, $P < 0.03$).

Comparison of blood pressure control and rate of decline in GFR in blacks versus non-blacks

Because of the reportedly higher risk for progressive renal failure in black patients, we compared blood pressure control and rate of decline in GFR slopes between races. Baseline and follow-up blood pressure and renal function for blacks and non-blacks is shown in Table 4. Baseline GFR and blood pressure were similar. During follow-up blood pressure was well controlled in both blacks and non-blacks; however, blacks had significantly higher blood pressure as compared to non-blacks. The mean difference in follow-up DBP between blacks and non-blacks was 6.4 mm Hg ($P < 0.0001$, 95% C.I. 3.29 to 9.51) and for MAP it was 5.3 mm Hg ($P < 0.01$, 95% C.I. 1.1 to 9.5). Mean follow-up DBP was ≤ 90 in 48 black and all 19 white patients and ≤ 95 mm Hg in all 56 blacks. Mean rate of decline in GFR in blacks was −0.16 ± 0.37 ml/min/1.73 m^2/year and in non-blacks it was −0.27 ± 0.76 ml/min/1.73 m^2/year ($P > 0.25$). After including baseline age, sex, serum creatinine, 24-hour urine protein and follow-up blood pressure as covariates in the model, the mean rates of decline for blacks was −0.04 ± 0.38 and for non-blacks −0.12 ± 0.78 ($P > 0.25$). These rates of decline in GFR were not significantly different from zero. Still, seven of nine patients who progressed to ESRD were black although the proportion of blacks developing ESRD (7 of 58) was not significantly different compared to non-blacks (2 of 19).

Patients not randomized

The 10 non-randomized patients were followed for a mean of 39 ± 3 months. Nine of 10 were male and all were black. At baseline, renal function was not different from the randomized groups; the mean serum creatinine was 2.2 ± 0.2 and mean GFR 37.3 ± 6 ml/min/1.73 m^2. As expected, baseline diastolic blood pressure (86 ± 2.5 mm Hg) was significantly higher in non-randomized patients compared to randomized patients ($P < 0.03$). Mean follow-up systolic blood pressure was 143 ± 3.8 and

Table 4. Blood pressure control and renal function at randomization and during follow-up: Blacks versus non-blacks with hypertensive nephrosclerosis

	Black ($N = 58$)	Non-black ($N = 19$)
Randomization		
Systolic BP *mm Hg*	123 ± 2	121 ± 2
Diastolic BP *mm Hg*	77 ± 1	74 ± 1
Mean arterial pressure *mm Hg*	92 ± 1	91 ± 1
Serum creatinine *mg/dl*	2.4 ± 0.1	2.2 ± 0.2
GFR *ml/min/1.73 m²*	37.7 ± 2.2	38.5 ± 4.0
Follow-up		
Systolic BP *mm Hg*	136 ± 2[a]	133 ± 3
Diastolic BP *mm Hg*	85 ± 1[b]	79 ± 1
Mean arterial pressure *mm Hg*	102 ± 1[b]	97 ± 2
GFR *mm Hg*	38.8 ± 2.8	33.0 ± 4.5
Rate of decline in GFR *ml/min/1.73 m²/year*	−0.16 ± 0.37	−0.27 ± 0.76
$1/S_{Cr}$ slope	−0.6 ± 0.5[c]	−3.4 ± 2.0
Serum creatinine final	2.8 ± 0.3	3.0 ± 0.6
Change in serum creatinine *mg/dl* (initial-final)	0.35 ± 0.19	0.82 ± 0.38
ESRD	7	2
Duration of follow-up	43.3 ± 1.7	35.1 ± 3.8

Units and abbreviations are the same as in Table 2. Mean rate of decline in GFR was estimated by the method of maximal likelihood in a mixed effects model.

P values: [a] < 0.0001; [b] < 0.01; [c] < 0.04

diastolic blood pressure was 91 ± 1.2. Mean follow-up DBP was not significantly different from the "conventional" group and mean GFR slope was not significantly different from either "strict" or "conventional" control groups. None of these patients experienced a doubling of serum creatinine, a 50% decline in GFR, ESRD or death.

Discussion

Chronic uncontrolled hypertension is believed to cause progressive renal damage in patients with hypertensive nephrosclerosis. Theoretically, long-term pharmacologic lowering of blood pressure to normal should slow or halt progressive renal damage in this condition. Previous prospective studies have been unable to show a benefit of blood pressure lowering on progression of renal disease in mild to moderate hypertensives [3–5, 7, 23]. However, these studies were not specifically designed to examine the impact of blood pressure control on renal function. Moreover, they did not examine the impact of different levels of blood pressure control on renal function and did not carefully evaluate the rate of change in GFR in treated hypertensive nephrosclerosis.

The present study was designed to measure the decline in GFR as a surrogate marker of progression of renal disease over a long period of time. The purpose was to determine whether long-term "strict" (65 to 80 mm Hg) versus "conventional" (85 to 95 mm Hg) control of diastolic blood pressure is associated with a slower decline in glomerular filtration rate in patients with hypertensive nephrosclerosis and established renal insufficiency who are at increased risk for disease progression [3–5, 26]. We found no significant difference in the mean rate of decline in GFR between "strict" and "conventional" blood pressure control groups despite a significant difference of 5.7 mm Hg in mean follow-up DBP (Table 2, Figs. 1 and 2). The mean rates of decline in GFR were relatively slow in both groups. Moreover, as shown in Figure 1, many patients in both groups appeared to have an improvement or stabilization in GFR during the period of follow-up. Our data suggest that lowering blood pressure to the range of 81 to 87 mm Hg in patients with mild to moderate renal insufficiency slows the rate of development of ESRD due to hypertensive nephrosclerosis. Widespread application of this quality of blood pressure reduction in hypertensive nephrosclerosis could dramatically reduce the incidence of ESRD in the United States.

Examination of the decline in GFR using the two slope model indicated the effect of altering blood pressure control during the first three months appeared to have an impact on the overall slope during the trial (Fig. 2). Thus, the average decline in GFR in the "conventional" group after the first three months was nearly twice that of the "strict" slope during the same period (Table 3). This observation suggests that patients assigned to the higher BP goal had a somewhat better short-term outlook but perhaps a somewhat greater risk of ESRD in the long-term. Still, the mean rate of decline in GFR after three months did not differ between groups; however, the number of patients in the trial was small and the variability in the GFR slope was considerable.

The fact that the mean difference in blood pressure was less than our goal of 10 mm Hg reflects difficulty in maintaining diastolic blood pressure below 80 mm Hg over a prolonged period of time, particularly in individuals with hypertensive nephrosclerosis on multiple medications (Tables 1). Still, achieving a mean DBP in the range of 81 mm Hg ("strict") or 87 mm Hg ("conventional") during periods up to 60 months was associated with a slow mean rate of progression of renal failure in the majority of patients with hypertensive nephrosclerosis (Figs. 1 and 2, Table 2). These rates are comparable to the rate of decline of GFR with age as reported in normotensive white males over age 40 [31].

An important question is whether the power of this study was too low to detect differences in the decline in GFR between blood pressure control groups. At the time this study was designed, the estimated mean difference in GFR between blood pressure intervention groups was projected to be on the order of 4 ml/min/year. It was calculated that approximately 80 patients would be needed to detect this difference with an α error of 5% and a power of 0.85, assuming a SD of about 6 ml/min/year in GFR slope. Although we observed that the variation in slope was in this range within both groups, to our surprise the rate of decline in GFR in both groups was much slower than expected. In other words the apparent low power of our study to detect a difference resulted primarily from the observed slow overall mean rate of decline in GFR even in the "conventional" group (95% C.I. for the difference = −1.60 to 1.09). Therefore, the assumed mean rate of decline in GFR was much larger than we observed. Although the power of the study is relatively low, we believe it rather remarkable that renal function deteriorated at such a slow mean rate in this study population.

Renal function was not preserved in all patients despite aggressive blood pressure control (Table 2, Figs. 1 and 3). Furthermore, renal failure progressed to ESRD in nine patients. Therefore, the overall slow rate of decline in GFR is due, in part, to an improvement in renal function in some patients that offset the progressive decline in others (Fig. 1). Moreover, since there was only a weak correlation between the rate of decline in GFR and the mean follow-up blood pressure, these findings suggest that

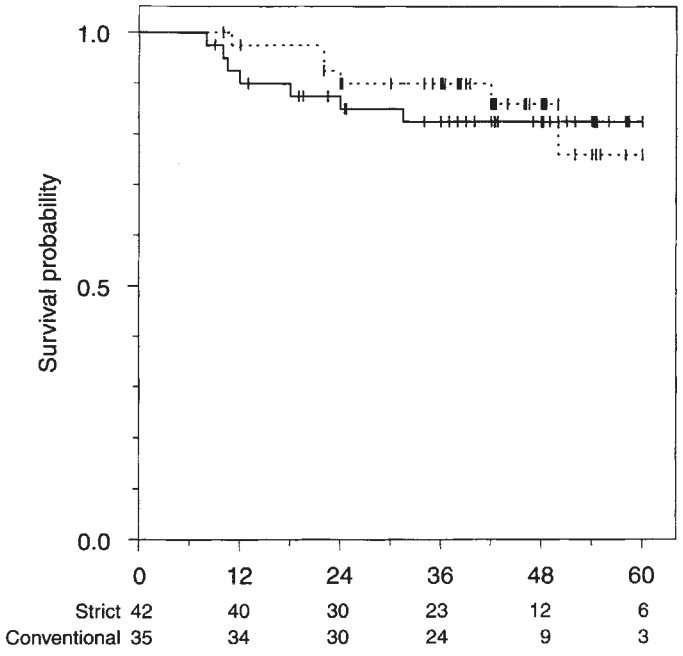

Fig. 3. *Kaplan-Meier plot of combined time-to-event analysis of outcome.* Symbols are: (____) "strict"; (. . .) "conventional" groups. The events include doubling of serum creatinine, 50% reduction in GFR, ESRD or death. Censored observations are denoted by vertical lines intersecting the survival function at the point of censoring. The number of patients in each group at each time point during follow-up is shown at the bottom of the Figure. There were no significant differences in time to event between groups.

other factors besides blood pressure control may be involved in renal disease progression in these patients.

We did not study a contemporaneous placebo-treated control group for comparison in view of the high rate of mortality in untreated patients. However, the high prevalence of documented non-renal cardiovascular complications prior to entry into the trial (Table 1) and the extraordinarily high-risk for future complications in this study population precluded an untreated control group on ethical grounds. Also, we did not measure the rate of progression of renal failure in our patients prior to randomization; therefore, we cannot prove that renal function would not have progressed at similar rates in the absence of antihypertensive therapy. However, to obtain such data prospectively would have required an observation period of at least two years, and standard medical care would have demanded controlling blood pressure at a level similar to our "conventional" control group, that is, diastolic blood pressure < 95 mm Hg.

We believe our patients would have progressed at an overall faster rate with no treatment or with a less aggressive approach to treatment. First, all our patients had reduced GFR, the most important risk factor for declining renal function [5]. Second, our patient population was composed of patients with characteristics associated with increased risk of ESRD [1, 3, 4, 7, 9, 11, 16, 21, 23, 32, 33]. Specifically, our study cohort had both a high prevalence of end-organ damage at baseline and a high proportion of black males (Table 1). In previous studies of hypertensive nephrosclerosis, GFR declined in 50 to 80% of untreated patients with hypertensive nephrosclerosis [3, 4], a rate considerably higher than that observed in the present study. Furthermore, the rate of deterioration of GFR in untreated patients ranges from 3 to 12 ml/min/year [3, 4] and from 2.3 to 4.5 ml/min/year in treated patients [30, 33, 34]. Moreover, in large studies of treated hypertensives with impaired renal function at baseline, renal function (estimated by S_{Cr}) deteriorates in 30% of white and 40% of black patients [5]. The mean rate of progression in these reports is 4 to 6 times higher than the present study. Finally, the incidence of ESRD in our population of patients with hypertensive nephrosclerosis was 9 of 77, or about 12%. Over an average period of 41 months, this computes to a rate of about 4% per year. In comparison, the rate of ESRD in VA cooperative trial in patients with poorly controlled hypertension and pre-existing renal disease was 30% over three years or a rate of 10%/year [4, 26]. Unfortunately, we know of no other comparable patient population screened and monitored during a similar period of observation with which to compare our data.

Baseline GFR was significantly lower in patients who developed ESRD as compared to those who did not. However, blood pressure control and duration of follow-up were similar for ESRD and non-ESRD patients. In addition, we found that patients with higher grade proteinuria (that is, > 500 mg/24 hr) had a faster decline in GFR, and the rate of decline was negatively correlated with the magnitude of proteinuria. Taken together, these findings suggest that long-term blood pressure control may not prevent progression to ESRD when renal function is severely impaired. Therefore, early detection and aggressive control of blood pressure before a critical amount of renal mass and function are lost may be extremely important in patients with hypertensive nephrosclerosis. Even though patients with apparently adequate control progressed to ESRD, the time to develop ESRD may have been prolonged because of aggressive blood pressure control. Further studies in patients with lower baseline GFR are needed to determine risk factors for progression.

Thirty-seven of 77 patients in this study were black males, a group that is recognized to be at highest risk for ESRD due to hypertension [1, 2, 4, 7, 12, 32]. Furthermore, seven of nine instances of ESRD occurred in black (1 male/6 female) participants, consistent with previous reports that blacks are at higher risk for ESRD. On the other hand, lowering diastolic pressure to an average level of 85 mm Hg in blacks (Table 4) was associated with stable or improved renal function in the majority of cases. It is possible that with longer follow-up, renal function would deteriorate significantly in these patients despite adequate blood pressure control. Because the overall mean rate of progression is slow, the results of this trial suggest that long periods (5 to 10 years) of follow-up should be employed in future studies focused on this issue.

The observed overall slow mean rate of progression of renal disease in patients at high risk for ESRD has not been reported previously for any population of patients with advanced renal disease. If confirmed, our observations have significant public health implications. They could lead to a reduction in the morbidity and mortality related to hypertension and to a reduction in health care costs [13]. Future treatments aimed at prevention of ESRD should take these findings into account. In addition, patient education programs designed to increase awareness may be useful for early recognition and treatment of this disease.

In conclusion, in this long-term, prospective randomized clinical trial of antihypertensive therapy in hypertensive nephrosclerosis, lowering diastolic blood pressure to a range of 81 to 87 mm Hg in patients with hypertensive nephrosclerosis is associated with stable or improving renal function in the majority of patients. The observed rate of ESRD of 4%/year is considerably lower than expected in untreated hypertensive nephrosclerosis [26]. Moreover, blacks of similar age, baseline renal function and long-term blood pressure control exhibited a rate of loss of renal function similar to non-blacks, suggesting that quality of blood pressure control may be the basis for differences in the reported incidence of ESRD between blacks and non-blacks. Our findings suggest that the development of ESRD due to hypertensive nephrosclerosis can be slowed or prevented in most patients, particularly if recognized and treated aggressively early in the disease process. These results have important implications for design of future trials and for delivery of health care in patients at high risk for ESRD.

Acknowledgments

This study was supported by NHLBI RO1-HL23670, NIH GCRC Grant MO1-RR006633 and by a grant from Merck, Sharp and Dohme. We also thank the following pharmaceutical companies for kindly providing medications for use in the study: Merck Sharp and Dohme, Pfizer, Stuart Pharmaceutical, E.R. Squibb & Sons, Inc., Marion Laboratories, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Smith Kline & French Laboratories, Hoechst-Roussel Pharmaceuticals Inc. CIBA-GEIGY Corp, Ayerst Laboratories, GEIGY Pharmaceuticals, and The Upjohn Co. We wish to acknowledge the assistance of the following of the physicians who participated in the care of the patients during this study: Dr. Mark Travis; members of the Dallas Nephrology Associates: Drs. Karl Brinker, Martin White, Mark Lerman, David Nesser, Thomas Gonwa, Alan R. Hull, Dewey Long, Ronald Prati, Steven Rinner, Michael Stephens, Michael Emmett, Pedro Vergne-Marini, Russell Silverstein, Andrew Fenves, Bruce Wall, Patsy Maikranz and George Rojas, and of the Tarrant County Nephrology Associates: Drs. Richard Mauk, Michael Stolz, J. Patrick Brennan, Kermit Olsen, Ry Mehta, and Charles Anderson. In addition, we thank Ms. Sally Thompson-Bell R.N. for technical and administrative assistance, and the secretarial and administrative assistance of Ms. Clara Ying in preparation of the manuscript.

Reprint requests to Robert D. Toto, M.D., Department of Internal Medicine, The University of Texas Southwestern Medical Center-Dallas, 5323 Harry Hines Blvd., Dallas, Texas 75235-8856, USA.

References

1. The National Institutes of Health U.S. Renal Data Systems Annual Report. *U S Renal Data Systems* 1993
2. BLYTHE WD, MADDUX FW: Hypertension as a causative diagnosis of patients entering end-stage renal disease programs in the United States form 1980–1986. *Am J Kid Dis* 28:33–37, 1991
3. MOYER JH, HEIDER C, PEVEY K, FORD RV: The effect of treatment on the vascular deterioration associated with hypertension, with particular emphasis on renal function. *Am J Med* 24:177–192, 1958
4. MAGEE JH, UNGER AM, RICHARDSON DW: Changes in renal function associated with drug or placebo therapy of human hypertension. *Am J Med* 36:795–804, 1964
5. SHULMAN NB, FORD CE, HALL WD, BLAUFOX D, SIMON D, LANGFORD HB, SCHNEIDER KA: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: Results from the Hypertension Detection and Follow-up study. *Hypertension* 13(Suppl I):I80–I93, 1989
6. BRECKENRIDGE A, DOLLERY CT, PARRY EHO: Prognosis of treated hypertension: Changes in life expectancy and causes of death between 1952 and 1967. *Quart J Med* 39:411–429, 1970
7. ROSTAND SG, BROWN G, KIRK KA, RUTSKY EA, DUSTAN HP: Renal insufficiency in treated essential hypertension. *N Engl Med* 320:684–688, 1988
8. WALKER GW, NEATON JD, CUTLER JA, NEUWIRTH R, COHEN JD: Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial. *JAMA* 268:3085–3091, 1992
9. ROSANSKY SJ, HOOVER DR, KING L, GIBSON J: The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. *Arch Intern Med* 150:2073–2076, 1990
10. RELMAN AS: Race and end-stage renal disease. *N Engl Med* 306:1290–1291, 1982
11. ROSTAND SG, KIRK KA, RUTSKY EA, PATE BA: Racial differences in the incidence of treatment for end-stage renal disease. *N Engl Med* 306:1276–1279, 1982
12. WHELTON PK, KLAG MJ: Hypertension as a risk factor for renal disease. *Hypertension* 13(Suppl I):I19–I27, 1993
13. EGGERS PW, CONNERTON R, MCMULLAN M: The medicare experience with end-stage renal disease: Trends in incidence, prevalence, and survival. *Health Care Fin Rev* 5:69–88, 1984
14. MCCLELLAN W, TUTTLE E, ISSA A: Racial differences in the incidence of hypertensive end-stage renal disease are not entirely explained by differences in the prevalence of hypertension. *Am J Kid Dis* 12:285–290, 1988
15. PETTINGER WA, MITCHELL HE: Minoxidil—An alternative to nephrectomy for refractory hypertension. *N Engl J Med* 289:167–173, 1973
16. MITCHELL HE, GRAHAM MR, PETTINGER WA: Renal function during long-term treatment of hypertension with minoxidil: Comparison of benign and malignant hypertension. *Ann In Med* 93:676–681, 1980
17. VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS: Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 202:116–122, 1967
18. MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP: Multiple Risk Factor Intervention Trial: Risk factor changes and mortality results. *JAMA* 248:1465–1467, 1982
19. MANAGEMENT COMMITTEE OF THE AUSTRALIAN THERAPEUTIC TRIAL IN MILD HYPERTENSION: Untreated mild hypertension: A report by the Management Committee of the Australian Therapeutic Trial in Mild Hypertension. *Lancet* i:185–191, 1982
20. VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS: Effects of treatment on morbidity in hypertension III. Influence of age, diastolic pressure and prior cardiovascular disease; Further analysis of side effects. *Circulation* XLV:991–1003, 1972
21. *National High Blood Pressure Education Program (NHBPEP) Working Group Report*. Bethesda, US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1990
22. LUKE RG: Can renal failure due to hypertension be prevented? *Hypertension* 18(Suppl 3):I139–I142, 1991
23. WOLFF FW, LINDEMAN RD: Effects of treatment in hypertension: Results of a controlled trial. *J Chron Dis* 19:227–240, 1966
24. BERGSTROM J, ALVESTRAND A, BUCHT H, GUTIERREZ A: Progression of chronic renal failure in man is retarded with more frequent clinical follow-up and better blood pressure control. *Clin Nephrol* 25:1–6, 1986
25. PETTINGER WA, LEE HC, REISCH J, MITCHELL HC: Long-term improvement in renal function after short-term "strict" blood pressure control in hypertensive nephrosclerosis. *Hypertension* 89:766–772, 1989
26. PERNEGER TV, KLAG JJ, FELDMAN HI, WHELTON PK: Projections of hypertension-related renal disease in middle-aged residents of the United States. *JAMA* 269:1272–1277, 1993
27. ISRAELIT A, LONG DL, WHITE MG, HULL AR: Measurement of glomerular filtration rate utilizing a single subcutaneous injection of 125I-iothalamate. *Kidney Int* 4:346–349, 1973

28. LEVEY AS: Measurement of renal function in chronic renal disease. *Kidney Int* 38:167–184, 1990
29. LAIRD NM, WARE JH: Random-effects models for longitudinal data. *Biometrics* 38:963–974, 1982
30. KLAHR S, LEVEY A, BECK G, CAGGIULA A, HUNSICKER L, KUSEK J, STRIKER G: The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. *N Engl Med* 330:877–884, 1994
31. LINDEMAN RD, TOBIN JD, SHOCK NW: Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 26:861–868, 1984
32. EASTERLING RE: Racial factors in the incidence and causation of end-stage renal disease (ESRD). *Trans Am Soc Artif Intern Organs* 23:28–33, 1977
33. SHULMAN NB: Epidemiology of hypertension in blacks, in *Hypertension in Blacks: Epidemiology, Pathophysiology and Treatment*, edited by HALL WD, SAUNDERS E, SHULMAN NB, Chicago, New York Medical Publishers, 1985, p 115
34. BRAZY PC, STEAD WW, FITZWILLIAM JF: Progression of renal insufficiency: Role of blood pressure. *Kidney Int* 35:670–674, 1989
35. ZUCCCHELLI P, ZUCCALA A, BORGHI M, FUSAROLI M, SASDELLI M, STALLONE C, SANNA G, GAGGI R: Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 42:452–458, 1992